[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XIV. Local Anesthetics Derived from α-Picoline

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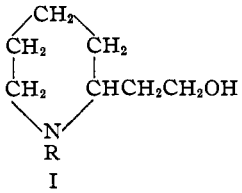
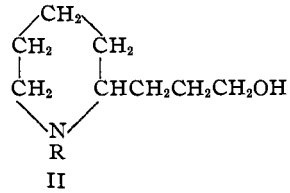
Previous papers[1] in this series have described the preparation of a number of local anesthetics from α-picoline. Since certain of these substances have shown very satisfactory pharmacological behavior, it seemed advisable to investigate other related types of compounds that could be prepared from this particular picoline which is now commercially available.

This paper describes the preparation and properties of the benzoate esters of the piperidyl substituted alcohols I, II and III in which R represents the alkyl groups, methyl, ethyl, *n*-propyl and *n*-butyl.



I



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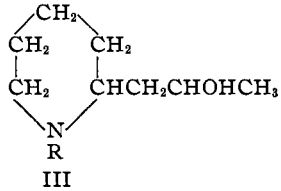
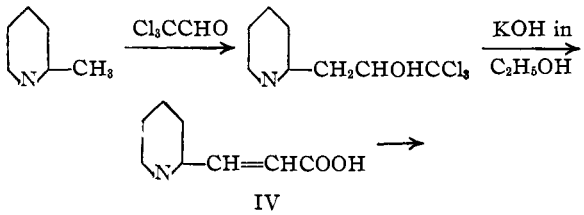


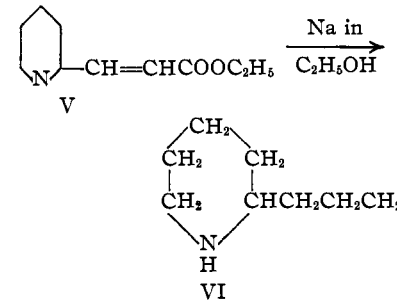
III

The alcohols of type (I) were prepared readily by alkylation of the secondary amine obtained by the reduction over Raney nickel of β-(2-pyridyl)-ethyl alcohol which was prepared from α-picoline and paraformaldehyde according to the method of Ladenburg.[2]

The preparation of alcohols of type II was much more difficult. The secondary amino alcohol (VI) which was alkylated to II was finally prepared through the following series of reactions

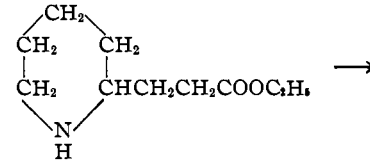


IV

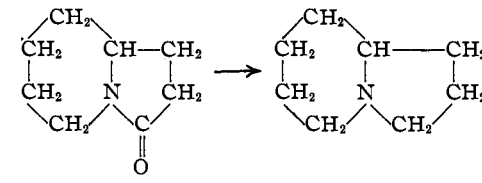


V VI

All attempts to carry out the reduction of V to VI catalytically were unsuccessful. Reduction of V over Raney nickel yielded the bicyclic amide, 3-keto-octahydropyrrocoline[3] (VIII) instead of the piperidyl propionic ester (VII). The catalytic reduction of the bicyclic amide VIII over copper–chromium oxide gave only the octahydropyrrocoline (IX).[3]



VII



VIII IX

For the preparation of alcohols of type III, 1,1,1-trichloro-2-hydroxy-3-(2-pyridyl)-propane (IV) was found to be the most advantageous starting material. While acetaldehyde may be condensed with α-picoline, the yields of the resulting 2-pyridyl-isopropyl alcohol (X) are extremely low (4–6%).[4] In contrast the trichloro compound (IV) may be obtained in yields as high as 70% of the theoretical. Attempts to reduce this trichloro compound have been reported in the literature. Feist[5] reported that all of his efforts to reduce IV to X were unsuccessful. Koller[6]

(1) McElvain, THIS JOURNAL, **49**, 2835 (1927); Bailey and McElvain, *ibid.*, **52**, 1633, 2007 (1930); Walters and McElvain, *ibid.*, **55**, 4625 (1933).

(2) Ladenburg, *Ann.*, **301**, 124 (1898).

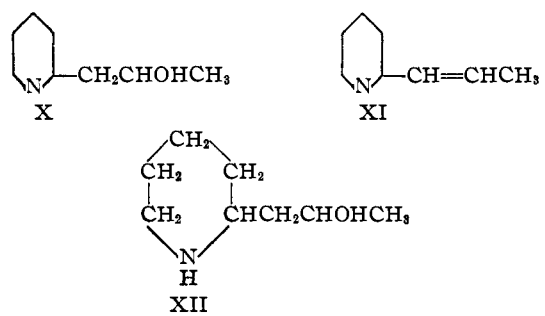
(3) Clemo and Ramage, *J. Chem. Soc.*, 2969 (1932); *cf.* also Löffler and Kain, *Ber.*, **42**, 102 (1909).

(4) *Cf.* Ladenburg, *Ann.*, **301**, 140 (1898); Meisenhimer and Mahler, *ibid.*, **462**, 301 (1928).

(5) Feist, *Arch. Pharm.*, **240**, 185 (1902).

(6) Koller, *Monatsh.*, **47**, 393 (1926).

reported the isolation of 2-propenylpyridine (XI) from the reaction of IV with zinc dust in aqueous methyl alcohol. After a study of the action of a variety of reducing agents (including hydrogen in the presence of catalytic platinum) on the trichloro compound (IV), it was found that sodium in absolute alcohol converted it to the desired piperidyl-isopropyl alcohol (XII) which could be isolated in yields of approximately 20% of the theoretical.



Details of the alkylation of the secondary amino alcohols and the benzoylation of the resulting tertiary amino alcohols, I, II and III, are given in the experimental part of the paper.

Pharmacological Report

The anesthetics which were prepared in this work were kindly tested pharmacologically by Mr. C. L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. The results of these tests are summarized in Table I and the discussion following. The benzoates of the tertiary amino-alcohols I, II and III with the varying R groups are listed by numbers. In the cases of nos. 4, 9, 10, 11 and 12 it was not possible to obtain crystalline hydrochlorides, so these benzoates were purified as the free bases by distillation and put into solution with hydrochloric acid before testing. The remainder of the compounds were obtained and used as crystalline hydrochlorides. For comparison, similar data for metycaine (γ-(2-methyl-piperidino)-propyl benzoate hydrochloride, Lilly) and procaine are given.

The toxicities of the compounds were determined by intravenous injection into mice and are reported as the minimum lethal dose (MLD), *i. e.*, the dose which causes the death of 50% of the animals injected. The anesthetic activities were determined by application of a 1% solution of the anesthetic to a rabbit's eye and noting the duration (in minutes) of the anesthesia produced.

TABLE I

PHARMACOLOGICAL PROPERTIES OF THE BENZOATES OF THE N-ALKYLPIPERIDYL SUBSTITUTED ALCOHOLS I, II AND III

No.	Benzoate of	R is	Intravenous toxicity to mice, MLD mg./kg.	Duration of anesthesia, min.
1	I	CH_3	49	5
2	I	C_2H_5	46	13
3	I	n-C_3H_7	27	16
4	I	n-C_4H_{10}	15	7
5	II	CH_3	31	13
6	II	C_2H_5	50	13
7	II	n-C_3H_7	29	13
8	II	n-C_4H_{10}	25	9
9	III	CH_3	15	10
10	III	C_2H_5	15	23
11	III	n-C_3H_7	15	18
12	III	n-C_4H_{10}	10	22
	Metycaine		29	13
	Procaine		60	4

It may be seen from the above data that the N-ethyl compound in each series (nos. 2, 6 and 10) shows the most favorable pharmacological properties. Nos. 10, however, has too high a toxicity to allow for a consideration of its relatively high anesthetic action. The other two N-ethyl derivatives (nos. 2 and 6) appear from the above tests to be definitely superior to metycaine. However, no. 6 appeared to be too irritating to the rabbit's cornea to merit any further investigation. The β-(2-N-ethylpiperidyl)-ethyl benzoate hydrochloride (no. 2) showed no more irritation to the rabbit's cornea than did metycaine and for this reason was tested by infiltration anesthesia on man. While it showed a considerably longer duration of anesthesia in these tests than did metycaine, it was found to be so much more irritating that it could not be considered as a good local anesthetic.

Experimental

β-(2-Pyridyl)-ethyl Alcohol.—This compound was prepared by heating 30 g. of paraformaldehyde and 200 cc. of α-picoline at 135–140° for nine hours under a pressure of 2000 pounds (133 atm.) of hydrogen in a steel bomb. After the excess of α-picoline was removed by distillation under diminished pressure, the pyridyl-ethyl alcohol was obtained as a water-white liquid boiling at 107–108° (7 mm.)[2] in yields of 32% of the theoretical.

β-(2-Piperidyl)-ethyl Alcohol.—A solution of 35.6 g. of the pyridyl-ethyl alcohol in 35 cc. of dry dioxane was reduced over Raney nickel under a hydrogen pressure of 260 atmospheres at 150–160°. After fractionation, 30.2 g. of material boiling at 105–108° (7 mm.) or 223–226° at atmospheric pressure was obtained.

This piperidine compound generally contained a small amount of the unreduced pyridine compound. To remove the latter the mixture was dissolved in dry ether and the

piperidine base precipitated as the carbamate by saturating the ether solution with carbon dioxide according to the method of Koenigs.[7] The base was recovered by treating the carbamate with a 50% solution of potassium hydroxide. The hydrochloride of the benzoyl derivative of β-(2-piperidyl)-ethyl alcohol melts at 182–183°.[2]

1,1,1 - Trichloro - 2 - hydroxy - 3 - (2 - pyridyl) - propane.—A mixture of 528 g. of chloral and 1050 cc. of α-picoline in a 3-liter flask was heated in an oil-bath at 112–113° for thirty-six to forty hours. The reaction mixture was cooled and the excess α-picoline was removed under a pressure of 10–20 mm. and at a temperature no higher than 95°. The black viscous residue was then poured, while still warm, into a 3-liter beaker and extracted with two 400-cc. portions of Skellysolve (b. p. 100–140°). The remaining insoluble black residue, which is mainly the hydrochloride of the condensation product, was then extracted with three 800-cc. portions of hot water and enough hydrochloric acid was added to each aqueous extract to make it acid to Congo red. The aqueous solution was filtered from the black insoluble material and the filtrate treated with sodium carbonate until it was alkaline. The trichloro base precipitated as an oil which soon solidified. The product was taken up in hot Skellysolve from which it crystallized on cooling in large light-brown crystals. This portion of the condensation product together with that obtained in the first extraction with Skellysolve were combined and recrystallized, after treatment with Norite, from this solvent.

The yield of 1,1,1-trichloro-2-hydroxy-3-(2-pyridyl)-propane so obtained amounted to 67% of the theoretical. Another treatment with Norite and recrystallization from Skellysolve gives a white product, m. p. 85–86°. This product has been prepared previously from α-picoline and chloral in amyl acetate[8] in yields of 40–47% of the theoretical.

Ethyl β-(2-Pyridyl)-acrylate (V).—1,1,1-Trichloro-2-hydroxy-3-(2-pyridyl)-propane was hydrolyzed to a mixture of β-(2-pyridyl)-acrylic acid and the corresponding lactic acid by the procedure of Einhorn.[9] It was unnecessary to separate these acids since it was found that the lactic acid yields the acrylic ester. The mixture of these acids was esterified directly by the procedure used by Clemo and Ramage[3] for the acrylic acid. The ester so obtained boiled at 142–145° (11 mm.).

γ-(2-Piperidyl)-propyl Alcohol.—In a 3-liter flask 213.5 g. of sodium was powdered under 400 cc. of xylene. After allowing the xylene to cool the flask was provided with an efficient stirrer, a five-foot (1.5-meter), wide-bore condenser and a dropping funnel. Then a solution of 40 g. of ethyl β-(2-pyridyl)-acrylate in 225 cc. of absolute alcohol was added to the sodium over a period of fifteen minutes. After this addition 550 cc. of absolute alcohol was added over a period of thirty minutes. When all of the sodium had disappeared, water was added until a clear solution resulted. The reaction mixture was then transferred to a 5-liter flask fitted with a short Vigreux column and the alcohol removed by distillation from a steam-bath. At this point two layers appeared. The upper xylene layer was removed and the lower aqueous alkaline layer was extracted with chloroform. The chloroform extracts were added to the xylene layer and the mixture distilled. After removal of the solvents, 13.5 g. (41.5%) of the 2-pyridylpropyl alcohol, b. p. 102–105° (3 mm.), was obtained. The hydrochloride and mercuric chloride complex with the hydrochloride melted at 127–128° and 182–183°, respectively.[10]

The catalytic reduction of ethyl β-(2-pyridyl)-acrylate (V) was carried out by Professor Homer Adkins. The hydrogenation of the acrylic ester to the corresponding pyridylpropionic ester takes place smoothly and quantitatively at 60° under 135 atmospheres of hydrogen with Raney nickel. The propionic ester was characterized as the picrate, m. p. 83–84°.[11] In an attempt to reduce this ester to the piperidylpropionic ester (VII), it was subjected to hydrogenation over Raney nickel at 200° and under 200 atmospheres of hydrogen. The only product that could be isolated was 3-keto-octahydropyrrocoline (VIII).[3] This product boils at 92–93° (1 mm.) and was obtained in yields of 93% of the theoretical. The reduction of 35 g. of this cyclic amide in 100 cc. of absolute alcohol over 5 g. of copper–chromium oxide catalyst at 250° under 250 atmospheres of hydrogen yielded 23 g. of octahydropyrrocoline (IX), b. p. 60–62° (22 mm.), and 156–158° at atmospheric pressure; m. p. of picrate, 223–226°.[3]

(2-Piperidyl)-isopropyl Alcohol.—In a 3-necked 3-liter flask 177 g. of sodium was powdered under 300 cc. of dry xylene. After cooling the xylene was decanted and replaced with 800 cc. of toluene. The flask was then fitted with an efficient stirrer, a 5-foot (1.5-meter), wide-bore condenser and a dropping funnel. A solution of 52 g. of 1,1,1-trichloro-2-hydroxy-3-(2-pyridyl)-propane in 225 cc. of absolute alcohol was added, with stirring, over a period of twenty-two minutes. After this addition, 550 cc. of absolute alcohol was added over a period of thirty minutes and the reaction mixture stirred until the sodium had disappeared. Water was then added until a clear solution resulted. The resulting solution was then distilled through a short Vigreux column from a steam-bath until no more distillate came over. The residue was then extracted with ether for thirty hours in a continuous extractor.

The ether was removed from the extract and the residues from five such runs as described above were combined and distilled. After the toluene had distilled 41.5 g. of a fraction boiling at 112–135° (11 mm.) was collected. This fraction on refractionation gave 30.5 g. of a distillate, b. p. 112–115° (11 mm.), which solidified completely, and 10 g. of a liquid product boiling at 130.5–132° (9 mm.). The lower boiling solid product was shown to be (2-piperidyl)-isopropyl alcohol. The yield was approximately 20% of the theoretical.

The product boiling at 130.5–132° (9 mm.) showed a neutral equivalent of 151 and was thought to be a diastereoisomeric racemate of the solid piperidylisopropyl alcohol (neutral equivalent 143). It reacted with 2 equivalents of acetic anhydride as did the solid compound. However, if these two products are diastereoisomeric racemates they

(7) Koenigs, *Ber.*, **35**, 1356 (1902).
(8) Koller, *Monatsh.*, **47**, 394 (1926).
(9) Einhorn, *Ann.*, **265**, 221 (1891).
(10) Löffler and Kain, *Ber.*, **42**, 3423 (1909).
(11) Clemo, *J. Chem. Soc.*, 1744 (1935).

TABLE II

PROPERTIES AND ANALYSES OF THE BENZOATES OF THE ALCOHOLS I, II AND III

No.	Formula	M. p., °C.	B. p., °C. (0.5 mm.)	d^{25}_{25}	$n^{25}D$	Neut. equiv. Calcd.	Neut. equiv. Found	Analyses, % Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
1	$C_{15}H_{22}O_2NCl$	139–140	.....	....	....	...	...	...	..	12.50	...	...	12.42
2	$C_{16}H_{24}O_2NCl$	148–150	.....	....	....	...	...	...	..	11.91	...	..	11.81
3	$C_{17}H_{26}O_2NCl$[a]	118–120	.....	....	....	...	...	...	..	11.37	...	..	11.30
4	$C_{18}H_{27}O_2N$[a]	.....	147–152	1.0169	1.5118	289	287.7	74.70	9.41	...	74.74	9.47	...
5	$C_{16}H_{24}O_2NCl$	135–137	.....	....	....	...	...	...	..	11.91	...	..	11.80
6	$C_{17}H_{26}O_2NCl$	114–116	.....	....	....	...	...	...	..	11.37	...	..	11.20
7	$C_{18}H_{28}O_2NCl$	139–141	.....	....	....	...	...	...	..	10.88	...	..	10.81
8	$C_{19}H_{30}O_2NCl$	132–134	.....	....	....	...	...	...	..	10.43	...	..	10.41
9	$C_{16}H_{23}O_2N$	.....	123–127[b]	1.0374	1.5159	261	262.6	73.53	8.87	...	73.42	9.10	...
10	$C_{17}H_{25}O_2N$	.....	118–122	1.0309	1.5142	275	275.5	74.15	9.15	...	74.09	9.23	...
11	$C_{18}H_{27}O_2N$	.....	139–141	1.0167	1.5097	289	289.7	74.70	9.41	...	74.62	9.49	...
12	$C_{19}H_{29}O_2N$	.....	143–147	1.0066	1.5067	303	302.1	75.20	9.64	...	75.35	9.58	...

[a] No. 3 is quite hygroscopic; no. 4 may be obtained as a crystalline hydrochloride but it is too hygroscopic to keep in this form. [b] Hess[18] reported this compound as boiling at 176–178° (16 mm.).

should give the same piperidyl acetone on oxidation. The solid compound yielded this ketone, the picrate of which has been described by Meisenheimer and Mahler.[12] The higher boiling liquid product, however, gave on oxidation a compound the picrate of which could not be caused to crystallize. No further work was done with this compound.

Preparation of the Tertiary Amino Alcohols I, II and III.—The secondary amino alcohols prepared above were alkylated by different procedures and the resulting tertiary amines distilled. These tertiary amines were not purified further since benzoylation readily removed any of the secondary amine that may have been present. The N-methyl compounds were prepared from the secondary amine, formaldehyde and formic acid according to the procedure of Hess.[13] When plenty of secondary amine was available the common alkylation procedure of allowing 2 moles of the secondary amine to react with 1 mole of the alkyl halide was used. When only small amounts of the secondary amine were available, Clemo and Metcalfe's method[14] of heating the secondary amine with the alkyl halide in the presence of potassium carbonate was used to advantage.

(12) Meisenheimer and Mahler, *Ann.*, **462**, 313 (1928).
(13) Hess, *Ber.*, **50**, 349 (1917).
(14) Clemo and Metcalfe, *J. Chem. Soc.*, 1520 (1937).

Benzoates of the Alcohols, I, II and III.—These benzoates were prepared by heating the alcohols with twice their volume of benzoyl chloride at 120–130° for about two hours. Dilution of the cooled reaction mixture with ether precipitated the hydrochloride of the benzoyl derivative which, if it were solid, was recrystallized to a constant melting point from an alcohol–ether mixture. In those cases in which the hydrochloride did not crystallize it was decomposed with 5% sodium hydroxide, taken up in ether and, after removal of the solvent, distilled. The β-(1-*n*-butyl-2-piperidyl)-ethyl benzoate and all of the benzoates derived from the alcohol III were in the latter group. The properties and analyses of these benzoates are summarized in Table II. The various benzoates are designated by the numbers that are used in Table I.

Summary

The preparation and properties, both pharmacological and physical, of a number of the benzoates of (1-alkyl-2-piperidyl) substituted ethyl, *n*-propyl and isopropyl alcohols are described. None of these compounds has proved to be a more effective local anesthetic than metycaine.

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